Chapter 15

Influenza

INFLUENZA IS A HIGHLY INFECTIOUS VIRAL ILLNESS. THE NAME, "influenza," originated in 15th century Italy, from an epidemic attributed to "influence of the stars." The first pandemic, or world-wide epidemic, that clearly fits the description of influenza was in 1580. At least four pandemics of influenza occurred in the 19th century, and 3 have occured in the 20th century. The pandemic of "Spanish flu" in 1918-1919 caused an estimated 21 million deaths worldwide.

Smith, Andrews, and Laidlaw isolated influenza A virus in ferrets in 1933, and Francis isolated influenza B virus in 1936. In 1940 Burnet discovered that influenza virus could be grown in embryonated hens' eggs. This led to the study of the characteristics of the virus and the development of inactivated vaccines. Evidence of the protective efficacy of inactivated vaccines was produced in the 1950s.

Influenza Virus

Influenza is a single-stranded, helically shaped, RNA virus of the orthomyxovirus family. Basic antigen types A, B, and C are determined by the nuclear material. Type A influenza has subtypes that are determined by the surface antigens hemagglutinin (H) and neuraminidase (N). Three types of hemagglutinin in humans (H1, H2, and H3) have a role in virus attachment to cells. Two types of neuraminidase (N1 and N2) have a role in virus penetration into cells.

Influenza A causes moderate to severe illness, and affects all age groups. The virus infects humans and other animals, such as pigs and birds.

Influenza

- **Highly infectious viral illness**
- **Epidemics reported since at least 1510**
- **At least 4 pandemics in 19th century**
- **Estimated 21 million deaths worldwide in pandemic of 1918-1919**
- **Virus first isolated in 1933**

Influenza Virus

- **Single-stranded RNA virus**
- **Family Orthomyxoviridae**
- **3 types: A, B, C**
- **Subtypes of type A determined by hemagglutinin and neuraminidase**

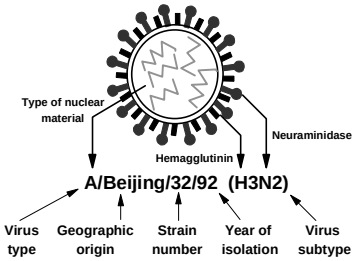
Influenza Virus Strains

- **Type A** - moderate to severe illness
  - animals and humans
  - all age groups
- **Type B** - milder epidemics
  - humans only
  - primarily affects children
- **Type C** - no epidemics
  - rarely reported in humans

Influenza B generally causes milder disease than type A, and primarily affects children. Influenza B is more stable than influenza A, with less antigenic drift and consequent immunologic stability. It affects only humans. It may be associated with Reye syndrome.

Influenza C is rarely reported as a cause of human illness, probably because most cases are subclinical. It has not been associated with epidemic disease.

Influenza Virus Schematic



The nomenclature to describe the type of influenza virus is expressed in this order: (1) virus type, (2) geographic site where it was first isolated, (3) strain number, (4) year of isolation, and (5) virus subtype.

Antigenic changes

Hemagglutinin and neuraminidase periodically change, apparently due to sequential evolution within immune or partially immune populations. Antigenic mutants emerge and are selected as the predominant virus to the extent that they differ from the antecedent virus, which is suppressed by specific antibody arising in the population. This cycle repeats continuously. In interpandemic periods, mutants arise by serial point mutations in the RNA coding for hemagglutinin. At irregular intervals of 10 to 40 years, viruses showing major antigenic differences from prevalent subtypes appear and, because the population does not have protective antibody against these new antigens, cause pandemic disease in all age groups.

Influenza Antigenic Changes

- **Structure of hemagglutinin (H) and neuraminidase (N) periodically change**
- **Shift** **Major change, new subtype Associated with pandemics**
- **Drift** **Minor changes, same subtype Associated with epidemics**

Antigenic shift is a major change in one or both surface antigens (H and/or N) that occurs at varying intervals. Antigenic shifts are probably due to genetic recombination between influenza A viruses, usually those that affect humans and birds. An antigenic shift may result in a worldwide pandemic if the virus is efficiently transmitted from person to person. The last major antigenic shift occurred in 1968 when H3N2 (Hong Kong) influenza suddenly appeared. It completely replaced the type A strain (H2N2, or Asian influenza) that had circulated throughout the world for the prior 10 years.

Examples of Influenza Antigenic Changes

- **Antigenic shift:**
  - **H2N2 circulated in 1957-1967**
  - **H3N2 appeared in 1968 and completely replaced H2N2**
- **Antigenic drift**
  - **In 1997, A/Wuhan/359/95 (H3N2) virus was dominant**
  - **A/Sydney/5/97 (H3N2) appeared in late 1997 and became the dominant virus in 1998**

Antigenic drift is a minor change in surface antigens that occurs between major shifts. Antigenic drift may result in epidemics, since incomplete protection remains from past exposures to similar viruses. Drift occurs in all three types of influenza virus (A,B,C). For instance, during most of the 1997-1998 influenza season, A/Wuhan/359/95 (H3N2) was the predominant influenza strain isolated in the United States. A/Wuhan was a drifted distant relative of the 1968 Hong Kong H3N2 strain. In the last half of the 1997-1998 influenza season, a drifted variant of A/Wuhan

appeared. This virus, named A/Sydney/5/97, was different enough from A/Wuhan (which had been included in the 1997-1998 vaccine) that the vaccine didn't provide much protection. Both A/Wuhan and A/Sydney circulated late in the 1997-1998 influenza season. A/Sydney became the predominant strain during the 1998-1999 influenza season, and was included in the 1998-1999 vaccine.

In the past 100 years, there have been 4 antigenic shifts that led to major **pandemics** (1889-1891, 1918-1920, 1957-1958, and 1968-1969). A pandemic starts from a single focus and spreads along routes of travel. Typically, there are high attack rates involving all age groups and mortality is usually markedly increased. Severity is generally not greater in the individual (except for the 1918-1919 strain), but because large numbers of people are infected, the number, if not the proportion, of severe and fatal cases will be large. Onset may occur in any season of the year. Secondary and tertiary waves may occur over a period of 1-2 years, usually in the winter.

Influenza Type A Antigenic Shifts

Year	Subtype	Severity of Pandemic
1889	H3N2	Moderate
1918	H1N1	Severe
1957	H2N2	Severe
1968	H3N2	Moderate
1977	H1N1	Mild

Typically in **epidemics**, influenza attack rates are lower than in pandemics. There is usually a rise in excess mortality. The major impact is observed in morbidity, with high attack rates and excess rates of hospitalization, especially for adults with respiratory disease. Absenteeism from work and school is high, with an increase in visits to health care providers. In the Northern Hemisphere, epidemics usually occur in late fall and continue through early spring. In the Southern Hemisphere, epidemics usually occur 6 months before or after those in the Northern Hemisphere.

Sporadic outbreaks can occasionally localize to families, schools, and isolated communities.

Pathogenesis

Following respiratory transmission, the virus attaches to and penetrates respiratory epithelial cells in the trachea and bronchi. Viral replication occurs, which results in the destruction of the host cell. Viremia does not occur. Virus is shed in respiratory secretions for 5 to 10 days.

Influenza
Pathogenesis

- **Respiratory transmission of virus**
- **Replication in respiratory epithelium with subsequent destruction of cells**
- **Viremia usually not demonstrable**
- **Viral shedding in respiratory secretions for 5-10 days**

Clinical Features

The **incubation period** for influenza is usually 2 days, but can vary from 1 to 5 days. The severity of influenza illness depends on the prior immunologic experience with antigenically related virus variants. In general, only around 50% of infected persons will develop the classic clinical symptoms of influenza.

Influenza
Clinical Features

- **Incubation period 1-5 days**
- **Abrupt onset of fever, myalgia, sore throat, nonproductive cough, headache**
- **Severity of illness depends on prior experience with antigenically related variants**
- **Case-fatality ~0.5-1 per 1000 cases**

"Classic" influenza disease is characterized by the abrupt onset of fever, myalgia, sore throat, and nonproductive cough. The fever is usually 101°-102°F, and accompanied by prostration. The onset of fever is often so abrupt that the exact hour is recalled by the patient. Myalgias mainly affect the back muscles. Cough is believed to be a result of tracheal epithelial destruction. Additional symptoms may include rhinorrhea (runny nose), headache, substernal chest burning and ocular symptoms (*e.g.*, eye pain and sensitivity to light).

Systemic symptoms and temperature usually last from 2 to 3 days, rarely more than 5 days. They may be decreased by such medications as aspirin or acetaminophen. **Aspirin should not be used for infants, children, or teenagers**, because they may be at risk for contracting Reye syndrome following an influenza infection. Recovery is usually rapid, but some may have lingering depression and asthenia (lack of strength or energy) for several weeks.

Complications

The most frequent complication of influenza is pneumonia, most commonly **secondary bacterial pneumonia** (*e.g.*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). **Primary influenza viral pneumonia** is an uncommon complication with a high fatality rate. **Reye syndrome** is a complication that occurs almost exclusively in children, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion which may progress to coma, due to swelling of the brain.

Influenza
Complications

- **Pneumonia**
  - **primary influenza**
  - **secondary bacterial**
- **Reye syndrome**
- **Myocarditis**
- **Death**

Other complications include **myocarditis** (inflammation of the heart), and **worsening of chronic bronchitis** and other chronic pulmonary diseases. **Death** is reported in 0.5-1 per 1000 cases. The majority of deaths occur in persons >65 years of age.

Impact of Influenza

Impact of Influenza

- **>20,000 excess deaths in each of 5 epidemics between 1972 and 1995**
- **>40,000 excess deaths in each of 6 epidemics**
- **>90% of deaths among persons 65 years of age or older**

An increase in mortality typically accompanies an influenza epidemic. Increased mortality results not only from influenza and pneumonia, but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza.

In studies of influenza epidemics occurring from 1972 through 1995 (years with only antigenic drift), excess deaths associated with influenza occurred during 19 of 23 influenza epidemics. An estimated 20,000 or more influenza-associated deaths occurred during five of these epidemics, and over 40,000 deaths occurred during six epidemics.

Over 90% of deaths attributed to influenza or pneumonia occurred among persons 65 years of age or older.

Approximately 110,000 hospitalizations per year are related to influenza. In nursing homes, the attack rate may be as high as 60%, with up to 30% fatality rates. The cost of a severe epidemic has been estimated to be $12 billion.

An influenza pandemic could affect up to 200 million people, and result in up to 400,000 deaths. The 1918-1919 influenza is believed to have resulted in the death of at least 500,000 Americans in less than a year.

Laboratory Diagnosis

The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community.

Influenza
Diagnosis

- **Clinical and epidemiological characteristics**
- **Isolation of influenza virus from clinical specimen (e.g., nasopharynx, throat, sputum)**
- **Significant rise in Influenza IgG by serologic assay (e.g., compliment fixation)**
- **Direct antigen testing for type A virus**

Virus can be isolated from throat and nasopharyngeal swabs obtained within 3 days of onset of illness. Culture is performed by inoculation of amniotic or allantoic sac of chick embryos or certain cell cultures that support viral replication. A minimum of 48 hours are required to demonstrate virus, and 1 to 2 additional days to identify the virus type. As a result, culture is helpful in defining the etiology of local epidemics, but not in individual case management.

Serologic confirmation of influenza requires demonstration of a significant rise in influenza IgG. The acute specimen should be taken less than 5 days from onset and a convalescent specimen taken 10-21 days, or, (preferably, 21 days) following onset.

Complement Fixation (CF) and Hemagglutination Inhibition (HI) are the serologic tests most commonly used. The key test is HI, which depends on the ability of the virus to agglutinate human or chicken erythrocytes and inhibition of this process by specific antibody. Diagnosis requires at least a 4-fold rise in antibody titer.

Recently, **rapid diagnostic testing for influenza A antigen** has become available and should permit those in office and clinic settings to assess the need for antiviral use in patients with influenza A infection in a more timely manner.

Influenza
Epidemiology

• Reservoir	Human, animals (type A only)
• Transmission	Respiratory Probably airborne
• Temporal pattern	Peak December - March in temperate areas May occur earlier or later
• Communicability	Maximum 1-2 days before to 4-5 days after onset

Epidemiology

Occurrence

Influenza occurs throughout the world.

Reservoir

Humans are the only known reservoir of influenza types B and C. Influenza A may infect both humans and animals.

Transmission

Influenza is transmitted via aerosolized or droplet transmission from the respiratory tract of infected persons. A less important mode of transmission of droplets is by direct contact.

Temporal pattern

Influenza peaks from December to March in temperate climates, but may occur earlier or later. It occurs throughout the year in tropical areas.

Communicability

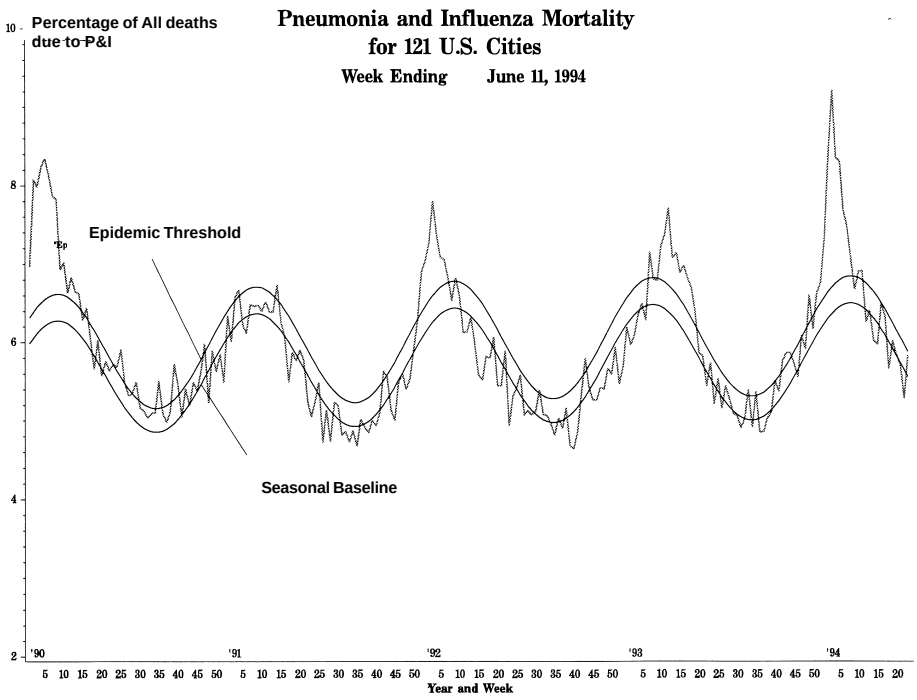
Maximum communicability occurs 1-2 days before onset to 4-5 days thereafter. There is no carrier state.

Secular Trends in the United States

A clear association exists between influenza and excess mortality. Ten thousand or more excess deaths have been documented in each of 19 different epidemics during the years 1957-1986; more than 40,000 excess deaths occurred in each of several recent epidemics. Outbreaks in nursing homes have shown attack rates as high as 60%, with case-fatality ratios as high as 30%.

There is a documented association between influenza and increased morbidity in “high-risk” adults. Hospitalization for adults with high-risk medical conditions increases 2-fold to 5-fold during major epidemics.

The impact of influenza in the United States is quantified by measuring pneumonia and influenza (P and I) deaths. Death certificate data are collected from 122 U.S. cities with populations of >100,000 (approximately 70,000,000). P and I deaths include all deaths for which pneumonia is listed as a primary or underlying cause, or for which influenza is listed on the death certificate.



An "expected" ratio of deaths due to P and I compared with all deaths for a given period of time is determined. The epidemic threshold for influenza seasons is generally estimated at 1.645 standard deviations above the values projected on the basis of a periodic regression model applied to observed P and I deaths for the previous 5-year period, excluding periods during influenza outbreaks.

Influenza epidemic activity is signaled when the ratio of deaths due to P and I exceeds the threshold ratio for 2 consecutive weeks.

Influenza Vaccine

Characteristics

The influenza vaccines available in the United States are composed of inactivated influenza virus. Two types of inactivated influenza virus vaccines are available. **Whole-virus vaccines** used today are prepared using chick embryo or allantoic fluid. The viruses are subjected to zonal gradient centrifugation or chromatography and subsequently inactivated. **Disrupted, or split-virus**

Influenza Vaccine

• Composition	Inactivated virus Whole or split (subvirion) Trivalent (H3N2, H1N1, B)
• Efficacy	Varies by similarity to circulating strain, age, underlying illness
• Duration of Immunity	<1 year
• Schedule	1 dose annually*

*2 doses for first vaccination of children <9 years

vaccines are prepared using organic solvents or detergents. Split vaccines are associated with fewer adverse events among children, perhaps because of disturbance of the spatial arrangement of the viral lipids. They are most useful in children 12 years of age or under, in whom whole-cell vaccines have prohibitive reactogenic effects.

A **cold attenuated live intranasal vaccine** has been under development for over 20 years. It is widely used in Russia for adult immunization. This vaccine is not yet licensed in the United States, but it may be available for children in the next few years.

In interpandemic years, vaccines are usually composed of viruses closely related antigenically to circulating strains of influenza A and B. In recent years, influenza vaccine has contained **three inactivated viruses** – two type A (H3N2 and H1N1), and one type B. The vaccine contains 15 µg of each hemagglutinin antigen per 0.5 ml dose. It contains thimerosal as a preservative and minute amounts of egg protein.

Influenza Vaccine Efficacy

- **70% to 90% effective among persons <65 years of age**
- **30%-40% effective among frail elderly persons**
- **50%-60% effective in preventing hospitalization**
- **80% effective in preventing death**

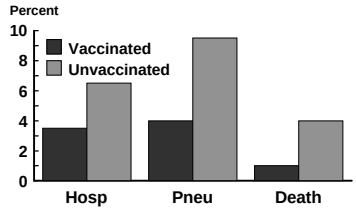
Immunogenicity and vaccine efficacy

For practical purposes, immunity following inactivated influenza vaccination rarely exceeds 1 year. Priming by prior infection with a closely related strain or prior vaccination enhances immunologic response after vaccination.

Influenza vaccine efficacy varies by the similarity of the vaccine strain(s) to the circulating strain, and the age and health status of the recipient. Vaccines are effective in protecting up to 90% of healthy young adult vaccinees from illness when the vaccine strain is similar to the circulating strain. However, the vaccine is only 30%-40% effective in preventing illness among frail elderly persons.

Although the vaccine is not highly effective in prevention of clinical illness among the elderly, it is effective in prevention of complications and death. Among elderly persons, the vaccine is 50%-60% effective in preventing hospitalization and 80% effective in preventing death. During a 1982-1983 influenza outbreak in Genesee County, Michigan, unvaccinated nursing home residents were four times more likely to die than vaccinated residents.

Complications of Influenza Among Nursing Home Residents



Genesee County, MI, 1982-1983

Vaccination Schedule and Use

Influenza activity peaks in temperate areas between late December and early March. Vaccine is most effective when it precedes exposure by no more than 2 to 4 months. It should be offered annually, beginning in September for routine patient visits. Organized campaigns for high-risk persons who are routinely accessible are optimally undertaken from October to mid-November. Vaccine may be given up to and even after influenza activity is documented in a region. Although most influenza vaccination activities should be completed by December (particularly for high-risk persons), providers should continue to provide vaccine throughout influenza season.

Timing of Influenza Vaccine Programs

- **Influenza activity peaks between late December and early March**
- **Optimal time for vaccination programs October through mid-November**
- **May start earlier if necessary**
- **Continue to vaccinate thoughout influenza season**

Influenza vaccine dosage, by age group--United States

Age Group	Product	Dosage	Number of Doses	Route
6-35 months	Split virus only	0.25 mL	1*or 2	IM
3-8 years	Split virus only	0.50 mL	1*or 2	IM
9-12 years	Split virus only	0.50 mL	1	IM
>12 years	Whole or split	0.50 mL	1	IM

*Only one dose is needed if the child received influenza vaccine during a previous influenza season.

One dose of influenza vaccine may be administered annually for persons 9 years of age or older. Children 6 months to 9 years of age receiving influenza vaccine for the first time should receive two doses administered at least 1 month apart.

Because of the lower potential for causing febrile reactions, **only split-virus vaccines should be used for children**. They may be labeled as "split," "subvirion," or "purified-surface-antigen" vaccine. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage.

Inactivated vaccine should be given by the intramuscular (IM) route. Other methods, such as intradermal, subcutaneous, topical, or mucosal should not be used.

Influenza vaccine is recommended for **all persons 50 years of age or older**, regardless of the presence of chronic illness. Other groups targeted for influenza vaccine include **residents of long-term care facilities**, **pregnant** women, and persons 6 months to 18 years of age receiving **chronic aspirin therapy** (because of the risk of Reye's syndrome following influenza infection).

Influenza Vaccine Recommendations

- **All persons 50 years of age or older**
- **Persons >6 months of age with chronic illness**
- **Residents of long-term care facilities**
- **Pregnant women**
- **Persons 6 months to 18 years receiving chronic aspirin therapy**

Influenza Vaccine Recommendations

- **Persons with the following chronic illnesses should be considered for influenza vaccine:**
  - **pulmonary (e.g., asthma, COPD)**
  - **cardiovascular (e.g., CHF)**
  - **metabolic (e.g., diabetes)**
  - **renal dysfunction**
  - **hemoglobinopathies**
  - **immunosuppression, including HIV infection**

Persons >6 months of age with chronic illness of many kinds should be vaccinated. These chronic illnesses include the following:

- pulmonary illnesses, such as emphysema, chronic bronchitis, or asthma
- cardiovascular illnesses, such as congestive heart failure
- metabolic diseases, including diabetes mellitus
- renal dysfunction
- hemoglobinopathies, such as sickle cell disease
- immunosuppression.

Pregnancy and Influenza Vaccine

- **Risk of hospitalization 4 times higher than nonpregnant women**
- **Risk of complications comparable to nonpregnant women with high risk medical conditions**
- **Vaccination recommended if ≥ 14 weeks gestation during influenza season**

Case reports and limited studies suggest that **pregnant women** may be at increased risk for serious medical complications of influenza as a result of increases in heart rate, stroke volume and oxygen consumption, decreases in lung capacity, and changes in immunologic function. A recent study found that the risk of hospitalization for influenza-related complications was more than 4 times higher for women in the second or third trimester of pregnancy than for nonpregnant women. The risk of complications for these pregnant women was comparable to that for nonpregnant women with high-risk medical conditions, for whom influenza vaccine has been traditionally recommended.

ACIP now recommends vaccination of women who will be in at least the 14th week of gestation during influenza season. Influenza season in the United States generally occurs in December through March. Therefore, women who become pregnant between March and December are vaccine candidates. Pregnant women who have high-risk medical conditions should be vaccinated before influenza season regardless of the stage of pregnancy.

HIV Infection and Influenza Vaccine

- **Persons with HIV at higher risk of complications of influenza**
- **Vaccine induces protective antibody titers in many HIV infected persons**
- **Transient increase in HIV replication reported**
- **Vaccine will benefit many HIV-infected persons**

Available data suggest that persons with **HIV infection** may have prolonged influenza illnesses and are at increased risk of complications of influenza. Many persons with HIV infection will develop protective antibody titers following influenza vaccine. In persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine may not induce protective antibody titers. A second dose of vaccine does not improve the immune response in these persons.

Recent studies have examined the effect of influenza vaccine on replication of HIV. Some studies have

demonstrated a transient increase in viral titer in the blood of vaccinated persons infected with HIV. This phenomenon has also been reported after other vaccines, such as tetanus toxoid and pneumococcal polysaccharide vaccines. Not all studies produced these findings; other investigators using similar methods have not documented increased HIV titers after influenza vaccination. Furthermore, although HIV titers may transiently increase, there is no evidence of deterioration in CD4 counts or progression of clinical HIV disease. Because influenza can result in serious illness and complications and because influenza vaccination may result in protective antibody titers, ACIP believes that influenza vaccination will benefit many persons with HIV infection.

Groups that have contact with high-risk persons should be vaccinated. These groups include **health care workers, employees of long-term care facilities, and household members of high-risk persons.** These individuals may be younger and healthier, and more likely to be protected from illness than elderly persons. **All health care providers should receive annual influenza vaccine.** Groups that should be targeted include physicians, nurses, and other personnel in hospitals and outpatient settings who have contact with high-risk patients in all age groups, and providers of home care to high-risk persons (*e.g.*, visiting nurses, volunteers).

Influenza Vaccine Recommendations

- **Health care providers, including home care**
- **Employees of long-term care facilities**
- **Household members of high-risk persons**

Persons who provide essential community services and **students or others in institutional settings** (*e.g.*, schools and colleges) may be considered for vaccination to minimize disruption of routine activities during outbreaks.

Influenza Vaccine Recommendations

- **Providers of essential community services**
- **Foreign travelers**
- **Students**
- **Anyone who wishes to reduce the likelihood of becoming ill from influenza**

Foreign travelers may want to be vaccinated. The risk of exposure to influenza during foreign travel varies, depending on season of travel, the mode of travel (*e.g.*, increased risk during cruises) and destination. Influenza can occur throughout the year in the tropics. In the Southern Hemisphere, influenza activity peaks in April-September. If not vaccinated the previous fall/winter, persons (especially those in high-risk groups) preparing to travel to the tropics at any time of the year or to the Southern Hemisphere during April-September, should be considered for influenza vaccination before travel. The most current available vaccine should be used.

Any person who wishes to lessen his/her chance of acquiring influenza infection may be vaccinated.

Adverse Reactions Following Vaccination

Influenza Vaccine Adverse Reactions

• Local reactions	15%-20%
• Fever, malaise	uncommon
• Allergic reactions	rare
• Neurological reactions	very rare

Local reactions are the most common adverse events following influenza vaccination. They include soreness, erythema, and induration at the site of injection. These events are transient, generally lasting 1 to 2 days. Local reactions are reported in 15%-20% of vaccinees.

Non-specific systemic symptoms including fever, chills, malaise, and myalgias are reported in <1% of vaccine recipients. These symptoms usually occur in those with no previous exposure to the viral antigens in the vaccine. They usually occur within 6-12 hours of vaccination and last 1-2 days. Recent reports indicate that systemic symptoms are no more common than in persons given a placebo injection.

Rarely, **immediate hypersensitivity, presumably allergic, reactions** (such as hives, angioedema, allergic asthma, or systemic anaphylaxis) occur after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component. The majority are most likely related to residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein may induce immediate hypersensitivity reactions among persons with severe egg allergy. Persons who have developed hives, had swelling of the lips or tongue, or experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to assist in determining whether influenza vaccination may proceed or should be deferred. Persons with documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs — including those who have had occupational asthma or other allergic responses from exposure to egg protein — may also be at increased risk for reactions from influenza vaccine, and similar consultation should be considered. Protocols have been published for influenza vaccination of patients who have egg allergies and medical conditions that place them at increased risk for influenza infection or its complications.

The potential exists for hypersensitivity reactions to any vaccine component. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not develop reactions to thimerosal administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When it has been reported, hypersensitivity to thimerosal has usually consisted of local delayed-type hypersensitivity reactions.

Unlike the 1976 swine influenza vaccine, subsequent vaccines prepared from other virus strains have not been clearly associated with an increased frequency of **Guillain-Barré syndrome (GBS**). However, obtaining a precise estimate of a small increase in risk is difficult for a rare condition such as GBS, which has an annual background incidence of only one to two cases per 100,000 adult population.

Among persons who received the swine influenza vaccine in 1976, the rate of GBS exceeded the background rate by less than one case per 100,000 vaccinations. Even if GBS were a true adverse event in subsequent years, the estimated risk for GBS was much lower than one per 100,000. Further, the risk is substantially less than that for severe influenza or its complications, which could be prevented by vaccination, especially for persons aged 65 years or older, and those with a medical indication for influenza vaccine.

Although the incidence of GBS in the general population is very low, persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than persons without such a history irrespective of vaccination. As a result, the likelihood of coincidentally developing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of GBS. Whether influenza vaccination might be causally associated with this risk for recurrence is not known. It seems prudent for persons known to have developed GBS within 6 weeks of a previous influenza vaccination to avoid subsequent influenza vaccination. For most persons with a history of GBS who are at high risk for severe complications from influenza the established benefits of influenza vaccination justify yearly vaccination.

Although influenza vaccination can inhibit the clearance of warfarin and theophylline, studies have failed to show any adverse clinical effects attributable to these drugs among patients receiving influenza vaccine.

Contraindications and Precautions to Vaccination

Persons with a **severe allergic reaction** to a previous dose of influenza vaccine, or to a vaccine component (*e.g.*, eggs) should not receive influenza vaccine.

Persons with a **moderate to severe acute illness** normally should not be vaccinated until their symptoms have decreased.

Influenza Vaccine
Contraindications and Precautions

- **Severe allergic reaction to vaccine component or following prior dose**
- **Moderate or severe acute illness**

Neither pregancy nor breastfeeding is a contraindication to influenza vaccination.

Vaccine Storage and Handling

Influenza vaccine is generally shipped in an insulated container with coolant packs. Although some brands of influenza vaccine can tolerate room temperature for a few days, CDC recommends that the vaccine be stored at refrigerator temperature (2°-8°C [35°-46°F]). **Influenza vaccine must not be frozen**.

Opened multidose vials may be used until the expiration date printed on the package if not visibly contaminated.

Year 2000 Objectives and Coverage Levels

Year 2000 objectives are to increase influenza vaccination levels to 60% or higher among high-risk populations (80% in residents of chronic care facilities) and to reduce epidemic-related pneumonia and influenza-related deaths among persons 65 years of age and older. In 1997, 66% of persons 65 years of age and older reported influenza vaccine in the previous year. Vaccination levels were lower in black and Hispanic persons than among non-Hispanic white persons.

Strategies for Improving Influenza Vaccine Coverage

Up to 75% of persons at high risk for influenza or who die from pneumonia and influenza may have received care in a physician's office during the previous year. One study indicated that all persons who died from pneumonia or influenza and did not reside in a nursing home, had at least one medical visit during the previous year.

Influenza Vaccine
Strategies to Improve Coverage

- **Ensure systematic and automatic offering of vaccine to high-risk groups**
- **Educate health care providers and patients**
- **Address concerns about adverse events**
- **Emphasize physician recommendation**

An average of less than 20% of persons in high-risk groups receive influenza vaccine each year. More effective strategies for delivering vaccine to high-risk persons, their health care providers, and household contacts are needed. Persons for whom the vaccine is recommended can be identified and immunized in a variety of settings.

Outpatient clinics and physicians' offices

Persons who should receive vaccine should be identified and their charts marked. Vaccine use should be promoted, encouraged and recommended beginning in September and continuing through the influenza season. Those without regularly scheduled visits should receive reminders.

Nursing homes and other residential long-term care facilities

Immunization should be routinely provided to all residents at one period of time immediately preceding the influenza season; consent should be obtained at the time of admission.

Acute-care hospitals and continuing care centers

Persons for whom vaccine is recommended who are hospitalized from September through March should be vaccinated prior to discharge.

In outpatient facilities providing continuing care to high-risk patients *(e.g.,* hemodialysis centers, hospital specialty-care clinics, outpatient rehabilitation programs), all patients should be offered vaccine shortly before the onset of the influenza season.

Visiting nurses and others providing home care to high-risk persons

Persons providing home care should identify high-risk patients and administer vaccine in the home, if necessary.

Facilities providing services to persons aged ≥ 65 years

Vaccine should be offered to all unvaccinated residents or attendees on site at facilities providing services to persons >65 years of age *(e.g.,* retirement communities, recreation centers). Education and publicity programs should also be conducted in conjunction with other interventions.

Health care for travelers

Indications for influenza vaccine should be reviewed prior to travel and vaccine offered, if appropriate.

Administrators of all of the above facilities and organizations should arrange for influenza vaccine to be offered to all personnel before the influenza season. Additionally, household members of high-risk persons and others with whom they will be in contact should receive written information about why they should receive the vaccine and where to obtain it.

Antiviral Agents for Influenza A

In the United States, four antiviral agents are approved for preventing or treating influenza: amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and rimantadine are effective against type A influenza only, and are approved by the Food and Drug Administration for both influenza A prophylaxis and treatment in persons 1 year of age and older.

Zanamivir and oseltamivir are members of a new class of drugs called neuraminidase inhibitors, and are active against both influenza type A and type B. Zanamivir is provided as a dry powder that is administered by inhalation. It is approved for treatment of uncomplicated acute influenza A or B in persons 12 years of age and older who have been symptomatic for no more than 2 days. Oseltamivir is provided as an oral capsule. It is approved for the treatment of uncomplicated influenza A or B in adults 18 years of age and older who have been symptomatic for no more than 2 days. Neither zanamivir nor oseltamivir is approved for prophylaxis of influenza infection.

Antiviral agents for influenza are an adjunct to vaccine and are not a substitute for vaccine. Vaccination remains the principal means for preventing influenza-related morbidity and mortality.

ACIP published a summary of the neuramanidase inhibitor drugs in December 1999. Additional information on amantadine and rimantidine can be found in the latest ACIP statement on influenza vaccine.

Nosocomial Influenza Control

Many patients in general hospitals, and especially in referral centers, are likely to be high-risk patients. Hospitalized susceptible patients may acquire influenza from patients, hospital employees, or visitors. The preferred method of control is to vaccinate high-risk patients and medical personnel prior to the outbreak.

During community influenza A activity, the use of antiviral prophylaxis may be considered for high-risk patients not immunized or immunized too recently to have protective antibody levels. Antivirals may also be considered for unimmunized hospital personnel. Other measures include restricting visitors with respiratory illness; cohorting patients with influenza for 5 days following onset of illness; and postponing elective admission of patients with uncomplicated illness.

Influenza Surveillance

Reasons for surveillance include (1) to monitor the prevalence of circulating strains and to detect new strains necessary for vaccine formulation; (2) to estimate influenza-related impact on morbidity, mortality, and economic loss; (3) to rapidly detect outbreaks; (4) to assist disease control through rapid preventive action (*e.g.*, chemoprophylaxis of unvaccinated high-risk patients).

CDC receives weekly surveillance reports from the states showing the extent of influenza activity. Reports are classified into four categories: (1) no cases, (2) sporadic, (3) regional (cases occurring in counties collectively contributing less than 50% of a state's population), (4) widespread (cases occurring in counties collectively contributing 50% or more of a state's population).

Influenza Surveillance

- **Monitor prevalence of circulating strains and detect new strains**
- **Rapidly detect outbreaks**
- **Assist disease control through rapid preventive action**
- **Estimate influenza-related morbidity, mortality and economic loss**

Sentinel Family Physician Network

Physicians nationwide provide weekly telephone information about the number of cases and hospitalizations that have occurred in their practices; a subgroup of physicians collect nasopharyngeal specimens from selected cases for submission to the Centers for Disease Control and Prevention (CDC) for culture confirmation.

Epidemiologic Surveillance Project (ESP)

The Epidemiologic Surveillance Project (ESP) was first operated for influenza during the 1987-1988 influenza season. Case reports of culture-confirmed influenza are submitted electronically to CDC from participating health departments. Additional case-specific information permits more detailed epidemiologic analysis than the other reporting systems.

Laboratory surveillance

Fifty-three World Health Organization (WHO) Collaborating Laboratories in the U.S. regularly submit reports on the number of specimens tested and the number and type of influenza viruses isolated for each week from early October through mid-May to the WHO Collaborating Center for Influenza at CDC.

Summary - Influenza

- **>20,000 deaths in epidemic years**
- **>90% of deaths in persons ≥65 years of age**
- **Routine vaccination**
- **Vaccine prevents complications**

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